REMARKS

Claims 21-32 presently appear in this case. Claims 22-24 have been withdrawn from consideration. No claims have been allowed. The official action of May 5, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating autoimmune and inflammatory diseases, and particularly for treating septic shock, by administering a TNF receptor in combination with DHEA.

Claims 21 and 25-29 have been rejected under 35 USC 112 because the specification, while being enabling for a method of treating septic shock by administration of a TNF receptor, or TBP-1, in combination with DHEA, does not reasonably provide enablement for a method of treating autoimmune and inflammatory diseases by administration of a TNF receptor, or TBP-1, in combination with DHEA. The examiner states that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to practice the invention commensurate in scope with these claims. The examiner states that there is not a nexus between the LPS model of septic shock and other inflammatory and autoimmune diseases. Therefore, one of skill in the art would not be able to predict that inflammatory diseases other than septic shock

and autoimmune diseases would be treated by administration of DHEA in combination with TNF receptor. This rejection is respectfully traversed.

The prior art is well aware that the administration of TNF receptor such as TBP-1 is effective against autoimmune and inflammatory diseases. TNF is known to mediate autoimmune and inflammatory diseases and TBP reduces that response by interfering with the interaction of TNF with its native receptor. In this regard, the examiner's attention is directed to the following attached abstracts:

> Louie et al, "Biological Response Modifiers in the Management of Rheumatoid Arthritis", Am. J. Health Syst Pharm. 60:346-355 (2003)
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> Bao et al, "Exogenous Soluble Tumor Necrosis Factor Receptor Type I Ameliorates Murine Experimental Autoimmune Neuritis", Neurobiol Dis. 12:73-81 (2003)
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> Wang et al, "Polyethylene Glycolated Recombinant TNF Receptor I Improves Insulitis and Reduces Incidence of Spontaneous and Cyclophosphamide-Accelerated Diabetes in Nonobese Diabetic Mice", Endocrinology 143:3490-7 (2002)
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> Su et al, "Reduction of Arthritis and Pneumonitis in Motheaten Mice by Soluble Tumor Necrosis Factor Receptor", Arthritis Rheum. 41:139-49 (1998)
>
> Hunger et al, "Prevention of Autoimmune Diabetes Mellitus in NOD Mice by Transgenic Expression of Soluble Tumor Necrosis Factor Receptor p55", Eur J Immunol. 27:255-61 (1997)
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> Hunger et al, "Inhibition of Submandibular and Lacrimal Gland Infiltration in Nonobese Diabetic Mice by Transgenic Expression of Soluble TNF-Receptor p55", J Clin Invest. 98:954-61 (1996)

Wooley et al; "Influence of a Recombinant Human Soluble Tumor Necrosis Factor Receptor FC Fusion Protein on Type II Collagen-Induced Arthritis in Mice", J Immunol. 151:6602-7 (1993)

Zaccone et al, "Autoimmune Thyroid Disease Induced by Thyroglobulin and Lipopolysaccharide is Inhibited by Soluble TNF Receptor Type I", Eur J Immunol. 32:1021-8 (2002)

Culy et al, "Etanercept: An Updated Review of its Use in Rheumatoid Arthritis, Psoriatic Arthritis and Juvenile Rheumatoid Arthritis", Drugs 62:2493-537 (2002)

Murray et al, "Recombinant Human Tumor Necrosis Factor Receptor (p75) Fc Fusion Protein (TNFR: Fc) in Rheumatoid Arthritis", Ann Pharmacother 31:1335-8 (1997)

Heilig et al, "Evaluation of Tumor Necrosis Factor (TNF) receptors and TNF Receptor Antibodies in Patients with Systematic Lupus Erythematodes, Progressive Systemic Sclerosis, and Mixed Connective Tissue Disease", J Clin Immunol. 13:321-8 (1993)

Thus, it is hoped that the examiner will agree that it was known that TNF receptors are effective for treating autoimmune and inflammatory diseases of a broad scope, as it is also known that TNF is known to mediate a wide range of autoimmune and inflammatory diseases. If it was known that TNF receptor, such as TBP-1, is useful alone for treating a broad range of autoimmune and inflammatory diseases, then there should not be reason to believe that combining this treatment with DHEA would prevent the effect of TBP-1. There is no art rejection, so it is not necessary to prove synergistic results in order to establish unobviousness under 35 USC 103. The combination of

TNF receptor and DHEA should be expected to be operable in treating autoimmune and inflammatory diseases for the same reason that the prior art expected that TNF receptor alone would be operable in doing so. Since there is no motivation to add DHEA for any reason, particularly for autoimmune and inflammatory diseases other than septic shock, there is no requirement that there be any showing of superior results with the addition of DHEA, nor is there a requirement for an enabling disclosure of synergistic results. Accordingly, the present disclosure is enabling because, in light of the state of the prior art, those of ordinary skill in the art would expect that the combination of TNF receptor with DHEA would be at least as effective in treating a broad range of autoimmune and inflammatory diseases as is the use of TNF receptor by itself, which was already known to be effective for this purpose.

Furthermore, the proof of unexpected results with septic shock was submitted only as a proof of concept that DHEA has a synergistic effect on the effectiveness of TNF receptor. As TNF receptor is known to be useful in treating a wide range of autoimmune and inflammatory diseases and as DHEA has been shown to synergize this effectiveness in one of these conditions, it is no longer unreasonable to believe that it will also synergize the effect of TNF in all of the other autoimmune

and inflammatory diseases which are already known to be effectively treated by TNF receptor.

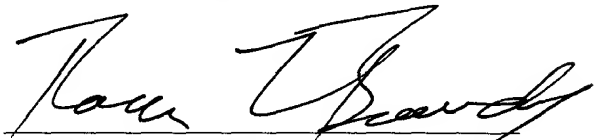
For all of these reasons, reconsideration and withdrawal of the enablement rejection is respectfully urged.

Once the present rejection is overcome, and the generic claim found to be allowable, the non-elected species claims 22-24 should be rejoined and allowed with the remaining claims. New claims 30-32 have now been added drawn to the embodiment that the examiner concedes to be allowable. Claim 32 is drawn to the presently non-elected species of TBP-2, but it should be entered and considered in light of the apparent allowability of a least sub-generic claim 30.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By 
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soluble-TNF-receptors and autoimmune/inflammatory diseases

Am J Health Syst Pharm. 2003 Feb 15;60(4):346-55.(Erratum in: Am J Health Syst Pharm.2003 Jun 1;60(11):1095.)

Biological response modifiers in the management of rheumatoid arthritis.

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The management of rheumatoid arthritis (RA) with biological response modifiers (BRMs) is reviewed. RA, an autoimmune disorder affecting 1-2% of the world's population, is characterized by inflammation of synovial tissues, joint swelling, stiffness, and pain that may progress to joint erosion. There is strong evidence that inflammatory mediators, such as tissue necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1), play a critical role in the pathogenesis of this disorder. IL-1-receptor antagonist (IL-1Ra) is produced in healthy subjects and helps to protect against the adverse effects associated with IL-1 overexpression. Administration of IL-1Ra or similar agents may reduce the effects of IL-1 and ameliorate inflammatory conditions. Traditional treatment of RA has been based on symptomatic management with non-steroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, and corticosteroids, each of which has substantial drawbacks in terms of effectiveness or adverse effects. Newer therapeutic strategies for blocking the biological effects of inflammatory cytokines include antibodies directed against **TNF** (e.g., infliximab), **soluble receptors** (e.g., etanercept) and receptor antagonists to IL-1 (anakinra) [corrected]. Clinical trials indicate that these BRMs may be more effective than traditional agents because they are able to alter joint remodeling in addition to attenuating symptoms. Anti-TNF therapies may be associated with increased risk for infections, sepsis, tuberculosis reactivation, demyelination disorders, and blood dyscrasias; anakinra appears to be safer. Combination therapy with BRMs may be more appropriate for RA than monotherapy. The role of BRMs in the treatment of RA will evolve as investigators learn more about the drugs and the disorder.

Neurobiol Dis. 2003 Feb;12(1):73-81.

Exogenous soluble tumor necrosis factor receptor type I ameliorates murine experimental autoimmune neuritis.

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Tumor necrosis factor (TNF) and its receptor (TNFR) have been strongly implicated in the pathogenesis of autoimmune disease. Soluble cytokine receptors may be shed naturally from cell membranes to inhibit cytokine activity. Experimental autoimmune neuritis (EAN) is a CD4 Th1 cell-mediated animal model of Guillain-Barre syndrome (GBS) in humans. In the present study, we investigated the effects of soluble TNFR type I (sTNFR I) in EAN induced in mice by P0 peptide 180-199 and Freund's complete adjuvant. Our data from two different therapeutic regimens indicate that the administration of sTNFR I effectively ameliorated the clinical and pathological signs of EAN, i.e., decreased its severity, shortened its duration, and reduced inflammatory cell infiltration into the peripheral nervous system. The suppression of clinical EAN was accompanied in vitro by a marked reduction in antigen-specific T-cell proliferation and IFN-gamma synthesis by spleen cells from **sTNFR I**-treated mice, compared to control mice treated with PBS. These data directly demonstrate a pivotal role for TNF in the development of EAN and also suggest that sTNFR I may have therapeutic potential for alleviating GBS in humans.

Endocrinology. 2002 Sep;143(9):3490-7.

Polyethylene glycolated recombinant TNF receptor I improves insulitis and reduces incidence of spontaneous and cyclophosphamide-accelerated diabetes in nonobese diabetic mice.

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We have conducted three studies to examine the role of TNFalpha in islet destruction in female nonobese diabetic mouse (NOD) mice, a model of human autoimmune diabetes, using polyethylene glycolated (PEGylated) soluble TNF receptor type I (PEG **sTNF-RI**) as TNFalpha antagonist. PEG sTNF-RI (3 mg/kg, sc) was given every other day to NOD mice from age wk 8 for 12 wk (study 1), from age wk 12 for 8 wk (study 2), or from age wk 8 for 3 wk, with cyclophosphamide (6 mg/mouse) injected at wk 9 to accelerate the onset of diabetes (study 3). Diabetic incidence was reduced (control vs. PEG sTNF-RI) from 68.7% (11 of 16) to 18.3% (3 of 16) in study 1, from 84.6% (11 of 13) to 28.5% (4 of 14) in study 2, and from 66.6% (8 of 12) to 23.1% (3 of 13) in study 3, respectively. The incidence of insulitis was also reduced from 91.6% (11 of 12) to 12.5% (2 of 16) in study 1 and from 100% (7 of 7) to 16.6% (2 of 12) in study 2 by PEG sTNF-RI. PEG sTNF-RI also largely preserved islet insulin content, reduced mRNA of inducible nitric oxide synthase and IL-6 in pancreases, and lowered plasma corticosterone, glycerol, and free fatty acid levels. These results confirm a pathogenic role of TNFalpha in mediating insulitis in NOD mice and suggest the prophylactic and therapeutic potential of PEG sTNF-RI for human autoimmune diabetes.

Arthritis Rheum. 1998 Jan;41(1):139-49. (Comment in: Arthritis Rheum. 2001 Jul;44(7):1721-2.)

Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor.

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OBJECTIVE. To determine the effects of anti-tumor necrosis factor (anti-TNF) therapy in the inflammatory and autoimmune disease in motheaten (me/me) mice, which exhibit a Fas apoptosis signaling defect. METHODS. Arthritis, pneumonitis, and mortality were analyzed in me/me mice treated with a novel, soluble, dimeric TNF receptor I (sTNFRI) molecule capable of high-affinity binding and neutralization of TNFalpha. RESULTS. Soluble TNFRI reduced serum levels of TNFalpha and led to a 2-fold increase in the lifespan of me/me mice, compared with the control treatment group. The treatment also reduced the development of the "motheaten" skin patches and alleviated pneumonitis and inflammatory lesions in the extremities of me/me mice compared with controls. However, the serum levels of IgM and IgM anti-double-stranded DNA autoantibody were comparable to those of untreated control mice. CONCLUSION. TNFalpha is an important cytokine involved in the pathogenesis of inflammatory disease in me/me mice, resulting in tissue damage and early mortality. Therapies directed at blocking TNF/TNFR interactions, such as the **sTNFRI** used in these experiments, may be effective in diseases associated with apoptosis defects leading to overutilization of the TNF/TNFR pathway.

Eur J Immunol. 1997 Jan;27(1):255-61.

Prevention of autoimmune diabetes mellitus in NOD mice by transgenic expression of soluble tumor necrosis factor receptor p55.

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The non-obese diabetic (NOD) mouse represents a relevant animal model of autoimmunity for insulin-dependent diabetes mellitus. The pathogenic role of tumor necrosis factor (TNF) in insulitis and beta cell destruction observed in these mice remains controversial, since injections of TNF or of anti-TNF antibodies have been reported to exert protection or acceleration of diabetes, depending on the timing of administration. In this study, we demonstrate that, in contrast to the non-transgenic littermates, NOD mice with permanent neutralization of TNF by high blood levels of soluble TNF receptor p55-human FcIgG3-fusion molecules resulting from the expression of a transgene are protected from spontaneous diabetes. They are also protected from accelerated forms of disease caused by transfer of NOD spleen cells or cyclophosphamide injections. This protection is associated with a marked decrease in the severity and incidence of insulitis and in the expression of the adhesion molecules MAdCAM-1 and ICAM-1 on the venules of pancreatic islets. These data suggest a central role for TNF-alpha in the mediation of insulitis and of the subsequent destruction of insulin-secreting beta-cells observed in NOD mice. They may be relevant to cell-mediated autoimmune diseases in general, in which treatment with **soluble TNF receptors** might be beneficial.

J Clin Invest. 1996 Aug 15;98(4):954-61.

Inhibition of submandibular and lacrimal gland infiltration in nonobese diabetic mice by transgenic expression of soluble TNF-receptor p55.

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Besides a prominent mononuclear cell infiltration of the islets of Langerhans, nonobese diabetic (NOD) mice also show massive cellular infiltrates of the submandibular and lacrimal glands concomitant with histological signs of tissue damage. To obtain insights into the mechanisms operative during the initiation and progression of tissue damage, we followed by in situ hybridization the appearance of cells containing mRNA of the gene encoding the proinflammatory cytokine TNF-alpha in the cellular infiltrates. Cells expressing TNF-alpha are mainly located in infiltrates, are absent in nonaffected glands, and are preferentially found among CD4 T cells. Secretion of TNF-alpha by gland-infiltrating cells was confirmed by an ELISPOT procedure. Direct evidence for an instrumental role of TNF-alpha in initiation and progression of submandibular and lacrimal gland infiltration is provided by the observed significant reduction in the extent of infiltration in nonobese diabetic mice transgenic for a soluble TNF receptor p55 fused to the Fc part of human IgG3. This protection from infiltration is paralleled by decreased expression of the adhesion molecules ICAM-1 and VCAM-1 in submandibular and lacrimal glands. These data suggest a central role of TNF-alpha in the initiation and progression of autoimmune tissue destruction of salivary glands and indicate beneficial effects of **soluble TNF receptors** in the treatment of organ-specific autoimmune diseases.

J Immunol. 1993 Dec 1;151(11):6602-7.

Influence of a recombinant human soluble tumor necrosis factor receptor FC fusion protein on type II collagen-induced arthritis in mice.

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A recombinant human TNF receptor Fc fusion protein (rhuTNFR:Fc) was assessed for antiarthritic activity using murine type II collagen-induced arthritis in mice. DBA/1 mice were immunized with bovine type II collagen and treated with rhuTNFR:Fc either from day 21 to day 28 (preventative protocol), or after disease onset for fourteen days (therapeutic protocol). Control mice received either sterile saline or human serum albumin injections. rhuT-NFR:Fc treatment significantly reduced both the incidence and the severity of collagen-induced arthritis in the preventative protocol. Mice receiving rhuTNFR:Fc therapeutically progressed to less severe disease than did control animals, and the arthritis index in rhuTNFR:Fc treated mice was significantly lower than the index in control mice from 7.5 weeks after treatment. The antibody response to collagen was significantly reduced by treatment with rhuTNFR:Fc in both the preventative and therapeutic protocols. No difference was observed in the proliferative response to type II collagen or Con A, but the response to LPS was significantly lower in rhuTNFR:Fc treated mice at the conclusion of both the preventative and therapeutic trials. The results suggest that **rhuTNFR**:Fc may have both immunosuppressive and antiarthritic properties in this experimental model, and may represent a useful approach to the treatment of autoimmune arthritis.

Eur J Immunol. 2002 Apr;32(4):1021-8.

Autoimmune thyroid disease induced by thyroglobulin and lipopolysaccharide is inhibited by soluble TNF receptor type I.

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Experimental autoimmune thyroiditis (EAT) is inducible in mice by immunization with thyroglobulin and adjuvant. Previous studies have shown that EAT is an autoimmune Th1-mediated disease but its characteristics differ with the adjuvant. Granulomatous lesions with marked follicular disruption develop following administration of thyroglobulin (Tg) and complete Freund's adjuvant (CFA) whereas when lipopolysaccharide (LPS) is used as the adjuvant only focal infiltrates of mononuclear cells are observed. The pro-inflammatory cytokine, TNF-alpha, is associated with Th1 autoimmune-mediated conditions. Cytokine antagonists have been used as potential therapeutic agents in several experimental autoimmune models. Soluble cytokine receptors belong to this category and may naturally be shed from cell membranes to inhibit cytokine activity. We show that the administration of the soluble TNF receptor type I (**sTNFR I**) in the induction of EAT has very different effects on the two models of induced autoimmune thyroiditis. sTNFR I treatment inhibits the induction of EAT only when mouse Tg is given with LPS not with CFA, suggesting an important difference in the pathogenic processes.

Drugs. 2002;62(17):2493-537.

Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis.

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Etanercept (**Enbrel**) is a subcutaneously administered biological response modifier that binds and inactivates tumour necrosis factor-alpha, a proinflammatory cytokine. In patients with early active rheumatoid arthritis, etanercept 25mg twice weekly was associated with a more rapid improvement in disease activity and a significantly greater cumulative response than methotrexate over 12 months of treatment in a randomised, double-blind trial. In addition, etanercept recipients showed a slower rate of radiographic progression and a more rapid improvement in quality of life than methotrexate recipients. The efficacy of etanercept was maintained at 3 years' follow-up. Etanercept was also significantly better than placebo at reducing disease activity in patients who had an inadequate response to previous treatment with disease-modifying antirheumatic drugs (DMARDs) in several well controlled trials. At study end (after 3 or 6 months' treatment), the percentage of patients achieving an American College of Rheumatology 20% (ACR20) response with etanercept (25mg or 16 mg/m(2) twice weekly) was 59 to 75% as monotherapy and 71% in combination with methotrexate; corresponding placebo response rates were 11 to 14% and 27%, respectively. Response has been maintained in patients who continued treatment for up to 5 years. In patients with psoriatic arthritis, etanercept 25mg twice weekly significantly reduced disease activity and improved skin lesions in two double-blind, placebo-controlled, 12- to 24-week trials. In the 24-week study, ACR20 response rates (50 vs 13%), psoriatic arthritis response rates (70 vs 23%) and the median improvement in skin lesions (33 vs 0%) were significantly greater in etanercept than in placebo recipients. In patients with polyarticular-course juvenile rheumatoid arthritis, etanercept resulted in improvements in all measures of disease activity and was significantly more effective than placebo at reducing disease flare. Eighty percent of patients receiving etanercept achieved a >or=30% reduction in disease activity over 7 months of treatment, and this was maintained for up to 2 years in a trial extension. Etanercept was generally well tolerated in children and adults in clinical trials; the most commonly occurring adverse effects included injection site reactions, infection, headache, rhinitis and dizziness. In conclusion, etanercept has emerged as an important new treatment option in inflammatory arthritis. Etanercept provides rapid and sustained improvements in disease activity in patients with early and DMARD-refractory rheumatoid arthritis and has been shown to inhibit radiographic progression in those with early disease. Well controlled studies have also demonstrated the efficacy of etanercept in patients with psoriatic arthritis or polyarticular-course juvenile rheumatoid arthritis.

Ann Pharmacother. 1997 Nov;31(11):1335-8.

Recombinant human tumor necrosis factor receptor (p75) Fc fusion protein (TNFR:Fc) in rheumatoid arthritis.

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BACKGROUND: Tumor necrosis factor (TNF) is the dominant mediator of the cytokine cascade that causes inflammation and joint destruction in rheumatoid arthritis. A new class of agents under investigation, the biologic TNF inhibitors, inhibits the activity of TNF. Recombinant human TNF receptor p75 Fc fusion protein (**TNFR:Fc; Enbrel**) blocks the activity of the cytokine TNF. The preclinical, Phase I, and Phase II data of TNFR:Fc in rheumatoid arthritis are reviewed in this article. METHODS: All available data on TNFR:Fc in rheumatoid arthritis were reviewed. These data included published literature and data on file at the manufacturer. RESULTS: TNFR:Fc has been effective in many models of inflammation, including animal models of rheumatoid arthritis and in clinical rheumatoid arthritis trials. Conclusions from a study with TNFR "knockout" mice (genetically altered mice incapable of producing TNFR proteins) demonstrated that p75 TNFR is a natural antagonist of TNF-mediated inflammation. A placebo-controlled, dose-escalation, Phase I trial evaluated the safety and efficacy of TNFR:Fc in patients with rheumatoid arthritis. There were no serious adverse effects reported. A Phase II, randomized, double-blind, placebo-controlled trial evaluated 180 patients with active rheumatoid arthritis whose previous therapy had failed. A dose-response relationship was observed in the number of tender and swollen joints; patients who received the highest dose (16 mg/m2) of TNFR:Fc had the greatest improvement. Treatment was generally well tolerated. TNFR:Fc is nonimmunogenic; no antibodies to TNFR:Fc have been detected thus far in human studies. CONCLUSIONS: Preliminary data indicate that TNFR:Fc is an excellent candidate for future long-term studies in the treatment of rheumatoid arthritis.

J Clin Immunol. 1993 Sep;13(5):321-8

Evaluation of soluble tumor necrosis factor (TNF) receptors and TNF receptor antibodies in patients with systemic lupus erythematodes, progressive systemic sclerosis, and mixed connective tissue disease.

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Two TNF binding proteins have been characterized as soluble fragments of TNF receptors. We measured the plasma concentrations of soluble type A (p75) and type B (p55) TNF receptors in patients with systemic lupus erythematodes (SLE), progressive systemic sclerosis (PSS), and mixed connective tissue disease (MCTD). In SLE and PSS patients plasma concentrations of both types of TNF receptors and in MCTD patients type A TNF receptors were significantly elevated compared to controls. Plasma concentrations of both soluble TNF receptors were highly correlated in SLE, PSS, and MCTD patients, indicating a possible coregulation of both TNF_ receptors. In contrast, soluble interleukin 2 receptor (sCD 25) plasma concentrations were not correlated and seem to be an independent parameter. The **soluble forms of the TNF receptors** neutralize TNF in cytotoxicity assays and are functionally active as TNF antagonists. In one patient with SLE, autoantibodies against type A TNF receptors were detected, TNF alpha, and TNF beta did not interfere with the autoantibody binding to the receptor.